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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,238	08/01/2005	Richard Hale	232432	4832

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EXAMINER	
WANG, CHANG YU	

ART UNIT	PAPER NUMBER
1649	

MAIL DATE	DELIVERY MODE
09/19/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,238	HALE ET AL.	
	Examiner	Art Unit	
	Chang-Yu Wang	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22,25,26 and 28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22,25,26 and 28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

RESPONSE TO AMENDMENT

Status of Application/Amendments/claims

1. Applicant's amendment filed Jul 3, 2007 s acknowledged. Claims 1-21, 23-24, 27, 29-49 are cancelled. Claims 22, 25, 26, 28 are pending and under examination in this office action.

2. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response.

3. Applicant's arguments filed on Jul 3, 2007 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections/Objections Withdrawn

4. The rejection of claims 21-28 and 49 under 35 U.S.C. 101 & 112 because of lack of utility is withdrawn in response to Applicant's cancellation of claims 21, 23, 24, 27 and 49 and Applicant's amendment to the claims by reciting a specific protein complex and activity to be measured in the claimed method. It is known in the art that γ-secretase comprising a high molecular weight protein complex comprising presenilin and nicastrin, which are encompassed in the protein complex disclosed in the instant method. Applicant identifies a protein complex comprising sambiastin-1, presenilin-1 and nicastrin. Although Applicant fails to disclose the functional relationship between the activity of sambiastin-1 and γ-secretase or the relationship between the activity of sambiastin-1 and presenilin or nicastrin, Applicant argues that the activity of sambiastin-

1 is also involved in γ-secretase activity. Applicant's argument is persuasive because regardless of the activity of sambiastin-1 in γ-secretase, amended claims are directed to a method of screening for a molecule increasing or decreasing γ-secretase activity, which can be measured via measuring the activity of a protein complex comprising presenilin and nicastrin. Thus the rejection under lack of utility is withdrawn.

The rejection of claims 21, 23, 24, 27 and 49 under 35 U.S.C. 112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is moot because claims 21, 23, 24, 27 and 49 are canceled.

The rejection of claims 21-24, 27, 28 and 49 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement is withdrawn in response to Applicant's cancellation of claims 21, 23, 24, 27 and 49 and Applicant's amendment to the claims by reciting a specific protein complex and activity to be measured in the claimed method.

The rejection of claim 49 under 35 U.S.C. 102(e) for being anticipated by U. S. Patent No. 6913919 (issued Jul 5, 2005, priority date Jun 17, 1998) is moot because the claim is canceled.

Claim Rejections/Objections Maintained

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 22, 25, 26 and 28 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while enabling for screening for a molecule that increases or decreases gamma-secretase activity of a protein complex comprising sambiasin-1 (SEQ ID NO:1), presenilin-1 (SEQ ID NO:2) and Nicastrin (SEQ ID NO:3), does not reasonably provide enablement for identifying a molecule that modulates a protein complex comprising sambiasin-1 (SEQ ID NO:1), presenilin-1 (SEQ ID NO:2) and Nicastrin (SEQ ID NO:3) for treatment or prevention of Alzheimer's disease as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. The rejection is maintained for the reasons made of record in the office action mailed 1/3/07, and as follows.

At p. 8 of the response, Applicant argues that amended claims are enabling because the specification enables a protein complex comprising sambiasin-1, presenilin-1 and nicastrin and use of the complex to screen for a molecule binding to the complex. Applicant's arguments have been fully considered but they are not persuasive.

In contrast, the amended claims recite determining gamma-secretase activity. However, the specification only discloses determining gamma-secretase activity by its activity in cleavage of APP and Notch. The specification fails to provide sufficient guidance as to what other substrates and other assays can be used to determine gamma secretase activity. The specification fails to teach what defined structure or features are requires for the substrates to be used in determining gamma-secretase activity. Thus, a skilled artisan cannot contemplate what other substrates or methods

can be used to determine gamma-secretase activity. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without such guidance, what substrates can be made to still maintain activity and used is unpredictable and the experimentation left to those skilled in the art is extensive and undue. See Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int. 1986). Thus, the skilled artisan cannot readily make and use the claimed invention as currently claimed without further undue experimentation.

In addition, claim 28 recites a drug for treatment or prevention of Alzheimer's disease. It is known in the art the protein complex comprising presenilin and nicastrin for gamma secretase is involved in cleavage of APP (i.e. Abeta processing), which relates to Alzheimer's disease. However, it is unknown whether sambiastin-1 would affect APP processing because the specification fails to teach what the function for sambiastin-1 is, and whether it is associated with Alzheimer's disease. Thus, it is unpredictable whether an agent affecting sambiastin-1 would affect Alzheimer's disease because the protein complex comprising presenilin and nicastrin is also involved in the Notch signaling pathway, which is related to developmental disorders caused by defects of the Notch pathway and is not related to Alzheimer's disease. Moreover, claim 28 recites prevention of Alzheimer's disease. Neither the specification nor the prior art teaches prevention of Alzheimer's disease by any given agent since the causes of Alzheimer's disease may be due to genetic mutation, which is a natural process and is not preventable. The specification fails to provide guidance as to how to identify which one of us at what time point would have Alzheimer's disease and can prevent it before the

disease happens. Since no guidance is provided to predict what time and what person would have Alzheimer's disease, it is not known how to identify a drug that can prevent the disease without further guidance to practice the claimed invention.

"The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004)"

Thus, the rejection of claims 22, 25, 26 and 28 under 35 U.S.C. §112, first paragraph, because the specification does not enable the invention commensurate in scope with the claims is maintained.

6. Claims 22, 25, 26 and 28 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is maintained for reasons made of record in the office action mailed 1/3/07, and as follows.

At p. 8 of the response, Applicant argues that amended claims meet the written description requirement because the claims have been amended to recite a specific protein complex comprising sambiasin-1, presenilin-1 and nicastrin, and recite determining gamma secretase activity. Applicant's arguments have been fully considered but they are persuasive.

In contrast, the specification fails to provide sufficient description to demonstrate Applicant's possession of all different physiological substrates to determine gamma secretase activity. The specification only describes APP and Notch as the substrate of gamma secretase. However, the claims are not limited to APP or Notch to be used in the claimed method for determining gamma secretase activity. The specification fails to describe what other substrates can be used in the claimed method. The specification fails to provide information as to what common structure or features that are required for the substrates to be used to determine gamma secretase activity.

A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Eli Lilly*, 119 F.3 at 1568, 43 USPQ2d at 1406. See also *Fiers*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (discussing *Amgen Inc. v.Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle &Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004).

Accordingly, the court held in *Univ. California v. Eli Lilly and Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) that:

"One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus. A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is".

and that:

"A description of a genus of cDNAs [products] may be achieved by means of a recitation of a representative number of cDNAs [products], *defined by nucleotide sequence*, failing in the scope of the genus or of a recitation of structural features common to the members of the genus, *which features constitute a substantial portion of the genus* [emphasis added]. This is analogous to enablement of a genus under 112, [first paragraph], by showing the enablement of a representative number of species within the genus. See *In re* Angstadt, 537 F.2d at 502-03, 190 USPQ at 218".

Since the structure and function of the genus of substrates for gamma secretase activity is unknown, a skilled artisan cannot envision the structural and functional

relationship between the claimed genus of substrates and the claimed invention. Thus, the specification fails to demonstrate that Applicant is in possession of the genus of substrates to be used in the claimed method to determine gamma secretase activity. See again MPEP 2163. Thus, the rejection of claims 22, 25, 26 and 28 under 35 U.S.C. 112, first paragraph, for failing to comply with the written description requirement is maintained.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 25 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

At p. 9 of the response, Applicant argues that amended claims have overcome the rejection because the claims have been amended to recite specific gamma-secretase and have removed the recitations such as function, activity and change. However, Applicant fails to address the recitation of "physiological substrate" in claim 25. There are two separate requirements set forth in the second paragraph of 35 USC 112: (A) the claims must set forth the subject matter that applicants regard as their invention; and (B) the claims must particularly point out and distinctly define the metes and bounds of the subject matter that will be protected by the patent grant. Claim 25 is indefinite because the disclosure fails to set forth the metes and bounds of what is encompassed within the definition of substrates. It is not clear what physiological

substrate can be used in the method and within the scope of the claims; and thus the claims are indefinite.

New Grounds of Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

8. Claim 26 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is indefinite because claim 26 recites the limitation "the amount" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 26 depends from claim 22. However, no such limitation of amount is recited in claim 22. Thus, claim 26 is indefinite.

Claim Rejections - 35 USC § 102/103

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 22, 25, 26 and 28 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over George-Hyslop et al. (WO200060069, published on Oct 12, 2000, priority Apr 1, 1999, which is also issued as US Patent No. 6,812,337). Claims 22, 25, 26 and 28 are also rejected under 35 U.S.C. 102(e) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over George-Hyslop et al. (US Patent No. 6,812,337, issued on Nov 2, 2004, priority Apr 1, 1999). The reasons of the rejection are based on citation from the reference of US 6,812,337.

George-Hyslop (WO'069 or US'337) teaches a method of screening for a molecule that modulates gamma-secretase activity by determining gamma-secretase activity of a complex comprising presenilin-1 and nicastrin (also named PAMP in George-Hyslop (WO'069 or US'337); i.e. as it relates to claim 1; see col. 4, lines 25-46; col.5, lines 1-33; col 18, line 40 to col 20, line 18; col.24, example 1 and col.31, example2). George-Hyslop (WO'069 or US'337) teaches screening for agonists or antagonists of nicastrin (PAMP) and identifying the function of nicastrin by isolating a protein complex comprising nicastrin, PS-1 and APP and mutants of PS-1 and

evaluating the levels of Abeta 40-42, which is to determine gamma-secretase activity because APP is processed into Abeta 40-42 by gamma-secretase (as in claims 22, 25, 26; see col. 28, line 27-col. 29, line 44). George-Hyslop (WO'069 or US'337) teaches the step of isolating the protein complex comprising presenilin-1 and nicastrin and contacting the complex with APP (i.e. a physiological substrate) in the presence or absence of a test agent (i.e. as it relates to claim 25; see col. 18, line 39 –col. 19 line 12; see col.24, line to col. 25, line 32; col. 28, line 9- col. 29, line 44; col. 31, example 2). George-Hyslop (WO'069 or US'337) teaches isolation of the protein complex comprising presenilin and nicastrin (PAMP) with anti-PS1, -PS2 and –APP antibodies (see col. 24, example 1). George-Hyslop (WO'069 or US'337) also teaches measuring the amount of the protein components of the complex (i.e. as in claim 26; see col. 26, lines 15-35; col. 28, line 27-col. 29, line 44; cols 27-28; col. 32, lines 20-42). George-Hyslop (WO'069 or US'337) George-Hyslop (WO'069 or US'337) further teaches identifying a candidate molecule for a potential drug for treatment of Alzheimer's disease (i.e. as it relates to claim 28; see col. 5, lines 15-20). Thus, claims 22, 25, 26 and 28 are anticipated by George-Hyslop (WO'069 or US'337).

Although George-Hyslop (WO'069 or US'337) does not explicitly teach the protein complex comprising presenilin-1, nicastrin and an additional protein such as sambiasin-1, the protein complex disclosed in George-Hyslop (WO'069 or US'337) comprising at least presenilin-1 and nicastrin and having gamma-secretase activity to cleave APP or Notch, which indicates that the protein complex comprises other additionally unknown proteins including unidentified sambiasin-1 (see col. 15, lines 10-

49). In addition, the protein complex disclosed in George-Hyslop (WO'069 or US'337) is isolated from human embryonic kidney cells HEK 293, which comprises sambiastin-1 as evidenced by US2002132252 (see below paragraph 12). Thus, comprising sambiasin-1 in the protein complex for gamma-secretase would be an inherent feature of the protein complex for gamma-secretase to cleave APP or Notch because the protein complex for gamma secretase is a high molecular weight protein complex and is a multimer (see col.6, lines 1-12; col.8, lines 38-44). In addition, the protein complex used in the claimed method is isolated from a cell or organism, indicating that in a physiological condition, the protein complex would inherently comprise presenilin-1, nicastrin and sambiastin-1 because if the activity of sambiasin-1 is for gamma-secretase activity, these three proteins would naturally form within the protein complex for gamma-secretase. Thus, the method of using the protein complex for gamma secretase to screen for a molecule modulating gamma secretase activity has been disclosed in George-Hyslop (WO'069 or US'337).

Note that

"There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. Schering Corp. v. Geneva Pharm. Inc., 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also Toro Co. v. Deere & Co., 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004)("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention."); Abbott Labs v. Geneva Pharms., Inc., 182 F.3d 1315, 1319, 51 USPQ2d 1307, 1310 (Fed.Cir.1999)" See MPEP § 2112 (II).

"The discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." Atlas Powder Co. v. Ireco Inc., 190 F.3d 1342,1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977). " See MPEP § 2112.01 [R-3].

In addition, it would have been obvious to one to one of ordinary skill in the art at the time the instant invention was made to isolate such protein complex and to identify other proteins within the complex for gamma secretase and to use the protein complex to identify an agent modulating gamma secretase activity because it is known in the art that the protein complex for gamma secretase is a multimer complex. The person of ordinary skill in the art would have been motivated and have expected success to isolate such protein complex comprising presenilin-1, nicastrin and sambiastin-1 and use the complex for the screening method because a protein complex comprising presenilin, nicastrin and other proteins for gamma secretase activity is known in the art and use of the protein complex for the screening an agent that modulates the gamma-secretase activity for a candidate drug for treatment of Alzheimer's disease has been disclosed in George-Hyslop (WO'069 or US'337) as set forth above. The claimed method is obvious over George-Hyslop (WO'069 or US'337) since it is known in the art to identify a molecule modulating gamma secretase and determining gamma secretase activity using a protein complex comprising presenilin and nicastrin for gamma secretase and the protein complex comprising presenilin and nicastrin and additional proteins is known as well. Identifying other unknown proteins including sambiastin-1 within the protein complex for determining gamma secretase activity does not render the claimed method patentable because it does not change the activity of the protein complex comprising presenilin and nicastrin for gamma secretase and for the screening method, which has been disclosed by George-Hyslop (WO'069 or US'337).

The sequence search results disclose as follows:

SEQ ID NO:3

```
AAY97549
ID   AAY97549 standard; protein; 709 AA.
AC   AAY97549;
DT   12-FEB-2001  (first entry)
DE   Human PAMP protein sequence.
KW   PAMP; human; presenilin associated membrane protein; immunogen;
     neurodegenerative disease; Alzheimer's disease; Lewy body variant;
     Parkinson's disease-dementia complex; neuropsychiatric disease;
     schizophrenia; age-associated memory loss; developmental disorder;
     neoplasm; diagnosis.
OS   Homo sapiens.
PN   WO200060069-A1.
PD   12-OCT-2000.
PF   03-APR-2000; 2000WO-CA000354.
PR   01-APR-1999;   99US-0127452P.
     30-DEC-1999;   99US-0173826P.
PA   (UTOR ) UNIV TORONTO GOVERNING COUNCIL.
PI   St George- Hyslop PH,  Fraser PE;
DR   WPI; 2000-665001/64.
     N-PSDB; AAA37885.
PT   Isolated presenilin associated membrane proteins and nucleic acids
     encoding them, useful for investigating and diagnosing Alzheimer's
     disease and other neurodegenerative diseases.
PS   Claim 2; Page 68-70; 79pp; English.
CC   This sequence is the human presenilin associated membrane protein (PAMP)
     of the invention. PAMP polypeptides may be used as an immunogen to
     generate antibodies that recognise the PAMP polypeptide. The PAMP
     nucleotide and protein sequence may also be used for diagnosing
     individuals who are at risk or who have a variety of neurodegenerative
     diseases (e.g. Alzheimer's disease, Lewy body variant, Parkinson's
     disease-dementia complex), neuropsychiatric diseases (e.g. schizophrenia,
     age-associated memory loss), developmental disorders, and neoplasms.
     These may further be used to deduce the structural organisation and
     topology of PAMP, to identify proteins which interact with PAMP either in
     concert with presenilin 1 (PS1) and PS2, or independently, and to create
     cell-free systems, transfected cell lines, and animal modes of
     neurodegenerative and other diseases
SQ   Sequence 709 AA;

  Query Match             100.0%;  Score 3687;  DB 3;  Length 709;
  Best Local Similarity   100.0%;  Pred. No. 0;
  Matches  709;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MATAGGGSGADPGSRGLLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MATAGGGSGADPGSRGLLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI 60

Qy         61 GCQSSISGDTGVIHVVEKEEDLQWVLTDGPNPPYMVLLESKHFTRDLMEKLKGRTSRIAG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GCQSSISGDTGVIHVVEKEEDLQWVLTDGPNPPYMVLLESKHFTRDLMEKLKGRTSRIAG 120

Qy        121 LAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLGNGLAYEDFSFPI 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 LAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLGNGLAYEDFSFPI 180

Qy        181 FLLEDENETKVIKQCYQDHNLSQNGSAPTFPLCAMQLFSHMHAVISTATCMRRSSIQSTF 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 FLLEDENETKVIKQCYQDHNLSQNGSAPTFPLCAMQLFSHMHAVISTATCMRRSSIQSTF 240

Qy        241 SINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDRVVVAATRLDSRSFFWNVAPGAESAVA 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 SINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDRVVVAATRLDSRSFFWNVAPGAESAVA 300

Qy        301 SFVTQLAAAEALQKAPDVTTLPRNVMFVFFQGETFDYIGSSRMVYDMEKGKFPVQLENVD 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 SFVTQLAAAEALQKAPDVTTLPRNVMFVFFQGETFDYIGSSRMVYDMEKGKFPVQLENVD 360

Qy        361 SFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATLEKSGAGVPAVILRRPNQSQ 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        361 SFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATLEKSGAGVPAVILRRPNQSQ 420

Qy        421 PLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWLSPEEDLNFV 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 PLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWLSPEEDLNFV 480

Qy        481 TDTAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKANNSWFQSILRQ 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 TDTAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKANNSWFQSILRQ 540

Qy        541 DLRSYLGDGPLQHYIAVSSPTNTTYVVQYALANLTGTVVNLTREQCQDPSKVPSENKDLY 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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```
Db        541 DLRSYLGDGPLQHYIAVSSPTNTTYVVQYALANLTGTVVNLTREQCQDPSKVPSENKDLY 600

Qy        601 EYSWVQGPLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYSTWTESRWKDIRARI 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 EYSWVQGPLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYSTWTESRWKDIRARI 660

Qy        661 FLIASKELELITLTVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY 709
              |||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 FLIASKELELITLTVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY 709


US-09-541-094-14
; Sequence 14, Application US/09541094
; Patent No. 6812337
; GENERAL INFORMATION:
;  APPLICANT: St.George-Hyslop, Peter H.
;  APPLICANT: Fraser, Paul E.
;  APPLICANT: University of Toronto
;  TITLE OF INVENTION: A novel presenilin associated membrane
;  TITLE OF INVENTION: protein and uses thereof
;  FILE REFERENCE: 1034/1F812-US1
;  CURRENT APPLICATION NUMBER: US/09/541,094
;  CURRENT FILING DATE: 2000-03-31
;  NUMBER OF SEQ ID NOS: 19
;  SOFTWARE: FastSEQ for Windows Version 3.0
; SEQ ID NO 14
;   LENGTH: 709
;   TYPE: PRT
;   ORGANISM: human
US-09-541-094-14

  Query Match           100.0%;  Score 3687;  DB 2;  Length 709;
  Best Local Similarity  100.0%;  Pred. No. 0;
  Matches  709;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MATAGGGSGADPGSRGLLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MATAGGGSGADPGSRGLLRLLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI 60

Qy         61 GCQSSISGDTGVIHVVEKEEDLQWVLTDGPNPPYMVLLESKHFTRDLMEKLKGRTSRIAG 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 GCQSSISGDTGVIHVVEKEEDLQWVLTDGPNPPYMVLLESKHFTRDLMEKLKGRTSRIAG 120

Qy        121 LAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLGNGLAYEDFSFPI 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 LAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCREIQWNSLGNGLAYEDFSFPI 180

Qy        181 FLLEDENETKVIKQCYQDHNLSQNGSAPTFPLCAMQLFSHMHAVISTATCMRRSSIQSTF 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 FLLEDENETKVIKQCYQDHNLSQNGSAPTFPLCAMQLFSHMHAVISTATCMRRSSIQSTF 240

Qy        241 SINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDRVVVAATRLDSRSFFWNVAPGAESAVA 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 SINPEIVCDPLSDYNVWSMLKPINTTGTLKPDDRVVVAATRLDSRSFFWNVAPGAESAVA 300

Qy        301 SFVTQLAAAEALQKAPDVTTLPRNVMFVFFQGETFDYIGSSRMVYDMEKGKFPVQLENVD 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 SFVTQLAAAEALQKAPDVTTLPRNVMFVFFQGETFDYIGSSRMVYDMEKGKFPVQLENVD 360

Qy        361 SFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATLEKSGAGVPAVILRRPNQSQ 420
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Qy        421 PLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWLSPEEDLNFV 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        421 PLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWLSPEEDLNFV 480

Qy        481 TDTAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKANNSWFQSILRQ 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        481 TDTAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFLIKANNSWFQSILRQ 540

Qy        541 DLRSYLGDGPLQHYIAVSSPTNTTYVVQYALANLTGTVVNLTREQCQDPSKVPSENKDLY 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        541 DLRSYLGDGPLQHYIAVSSPTNTTYVVQYALANLTGTVVNLTREQCQDPSKVPSENKDLY 600

Qy        601 EYSWVQGPLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYSTWTESRWKDIRARI 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        601 EYSWVQGPLHSNETDRLPRCVRSTARLARALSPAFELSQWSSTEYSTWTESRWKDIRARI 660

Qy        661 FLIASKELELITLTVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY 709
              |||||||||||||||||||||||||||||||||||||||||||||||||
Db        661 FLIASKELELITLTVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY 709
```

Conclusion

11. NO CLAIM IS ALLOWED.

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

SEQ ID NO:1

ID ABU59141 standard; protein; 247 AA.
AC ABU59141;
DT 28-APR-2003 (first entry)
DE Novel human secreted or transmembrane protein PRO1141.
KW Human; PRO; hypertrophy of neonatal heart; angiogenesis; wound healing; cardiac insufficiency disorder; cancer; tumour; immune response; adrenal cortical capillary endothelial growth; c-fos induction; vascular endothelial growth factor inhibition; VEGF inhibition; endothelial cell growth inhibitor; T-lymphocytes stimulation; retinal neurons cell survival; rod photoreceptor cell survival; retinal disorder; retinitis pigmentosum; kidney disorder; mammalian kidney mesangial cell proliferation; Berger disease; dermatitis; herpetiformis; Crohn's disease; chondrocyte proliferation; chondrocyte redifferentiation; sports injury; arthritis.
OS Homo sapiens.
PN US2002132252-A1.
PD 19-SEP-2002.
PF 14-NOV-2001; 2001US-00990442.
PR 16-JUN-1997; 97US-0049787P.

PA (GETH) GENENTECH INC.
PI Ashkenazi AJ, Baker KP, Botstein D, Desnoyers L, Eaton DL;
PI Ferrara N, Fong S, Gerber H, Gerritsen ME, Goddard A, Godowski PJ;
PI Grimaldi JC, Gurney AL, Kljavin IJ, Napier MA, Pan J, Paoni NF;
PI Roy MA, Stewart TA, Tumas D, Watanabe CK, Williams PM, Wood WI;
PI Zhang Z;
DR WPI; 2003-247083/24.
N-PSDB; ABX80312.
PT Novel isolated PRO polypeptides e.g., PRO826, PRO1068, PRO1184, PRO1346 and PRO1375, which stimulate proliferation of stimulated T-lymphocytes are therapeutically useful for enhancing immune response and in cancer treatments.
PS Claim 12; Fig 220; 648pp; English.
CC The invention describes an isolated human PRO polypeptide. The PRO polypeptides are useful in detecting PRO polypeptides in a sample, in linking a bioactive molecule to a cell expressing a PRO polypeptide, and in modulating at least one biological activity of a cell expressing a PRO polypeptide. PRO1312 stimulates hypertrophy of neonatal heart and is thus useful for treating cardiac insufficiency disorders. PRO1154 and PRO1186 stimulate adrenal cortical capillary endothelial growth, and PRO536, PRO943, PRO828, PRO826, PRO1068 or PRO535, PRO826, PRO819, PRO1126, PRO1360 and PRO1387 induce c-fos in endothelial cells, and are thus useful for treating conditions or disorders where angiogenesis would be beneficial, e.g. wound healing and antagonist of this polypeptide are useful for treating cancerous tumours. PRO812 inhibits vascular endothelial growth factor (VEGF) stimulated proliferation of endothelial cells and is thus useful for inhibiting endothelial cell growth in mammals which would be beneficial in inhibiting tumour growth. PRO826, PRO1068, PRO1184, PRO1346 and PRO1375 stimulate proliferation of stimulated T-lymphocytes and are therapeutically useful for enhancing immune response. PRO828, PRO826, PRO1068 or PRO1132 enhance survival of retinal neurons cells (PRO1132 is also enhances survival/proliferation of rod photoreceptor cells) and therefore are useful for treating retinal disorders of injuries, e.g. retinitis pigmentosum, AMD. PRO819, PRO813

and PRO11066 induce proliferation of mammalian kidney mesangial cells, and therefore are useful for treating kidney disorders associated with decreased mesangial cell function such as Berger disease or other nephropathies associated with dermatitis, herpetiformis or Crohn's disease. PRO1310, PRO844, PRO1312, PRO1192 and PRO1387 induce the proliferation and/or redifferentiation of chondrocytes in culture and are thus useful for treating sports injuries, and arthritis. This is the amino acid sequence of a novel human PRO protein
SQ Sequence 247 AA;

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  Query Match             100.0%;  Score 1256;  DB 6;  Length 247;
  Best Local Similarity   100.0%;  Pred. No. 8.8e-131;
  Matches  247;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MGAAVFPGCTFVAFGPAFALFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILVHVT 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MGAAVFPGCTFVAFGPAFALFLITVAGDPLRVIILVAGAFFWLVSLLLASVVWFILVHVT 60

Qy         61 DRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYV 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 DRSDARLQYGLLIFGAAVSVLLQEVFRFAYYKLLKKADEGLASLSEDGRSPISIRQMAYV 120

Qy        121 SGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTFWGVVFFD 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 SGLSFGIISGVFSVINILADALGPGVVGIHGDSPYYFLTSAFLTAAIILLHTFWGVVFFD 180

Qy        181 ACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQ 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 ACERRRYWALGLVVGSHLLTSGLTFLNPWYEASLLPIYAVTVSMGLWAFITAGGSLRSIQ 240

Qy        241 RSLLCKD 247
              |||||||
Db        241 RSLLCKD 247
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SEQ ID NO:2

```
US-09-227-725A-1
; Sequence 1, Application US/09227725A
; Patent No. 6383758
; GENERAL INFORMATION:
;  APPLICANT:  St. George-Hyslop, Peter H.
;  APPLICANT:  Rommens, Johanna
;  APPLICANT:  Fraser, Paul E.
;  TITLE OF INVENTION:  Alzheimer's Related Proteins and Methods
;  TITLE OF INVENTION:  of Use
;  FILE REFERENCE:  1034/1F810-US1
;  CURRENT APPLICATION NUMBER: US/09/227,725A
;  CURRENT FILING DATE:  1999-01-08
;  NUMBER OF SEQ ID NOS:  4
;  SOFTWARE:  FastSEQ for Windows Version 3.0
; SEQ ID NO 1
;   LENGTH: 467
;   TYPE: PRT
;   ORGANISM: Homo Sapien
US-09-227-725A-1

  Query Match             100.0%;  Score 2393;  DB 2;  Length 467;
  Best Local Similarity   100.0%;  Pred. No. 7.1e-235;
  Matches  467;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQGNSR 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQGNSR 60

Qy         61 QVVEQDEEEDEELTLKYGAKHVIMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTE 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 QVVEQDEEEDEELTLKYGAKHVIMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTE 120

Qy        121 DTETVGQRALHSILNAAIMISVIVVMTILLVVLYKYRCYKVIHAWLIISSLLLLFFFSFI 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 DTETVGQRALHSILNAAIMISVIVVMTILLVVLYKYRCYKVIHAWLIISSLLLLFFFSFI 180

Qy        181 YLGEVFKTYNVAVDYITVALLIWNFGVVGMISIHWKGPLRLQQAYLIMISALMALVFIKY 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 YLGEVFKTYNVAVDYITVALLIWNFGVVGMISIHWKGPLRLQQAYLIMISALMALVFIKY 240

Qy        241 LPEWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAE 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 LPEWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAE 300

Qy        301 GDPEAQRRVSKNSKYNAESTERESQDTVAENDDGGFSEEWEAQRDSHLGPHRSTPESRAA 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GDPEAQRRVSKNSKYNAESTERESQDTVAENDDGGFSEEWEAQRDSHLGPHRSTPESRAA 360
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Qy        361 VQELSSSILAGEDPEERGVKLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGLCL 420
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Db        361 VQELSSSILAGEDPEERGVKLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGLCL 420

Qy        421 TLLLLAIFKKALPALPISITFGLVFYFATDYLVQPFMDQLAFHQFYI 467
              |||||||||||||||||||||||||||||||||||||||||||||||
Db        421 TLLLLAIFKKALPALPISITFGLVFYFATDYLVQPFMDQLAFHQFYI 467


US-08-888-077A-2
; Sequence 2, Application US/08888077A
; Patent No. 6020143
;  GENERAL INFORMATION:
;    APPLICANT:  ST. GEORGE-HYSLOP, PETER H
;    APPLICANT:  ROMMENS, JOHANNA M
;    APPLICANT:  FRASER, PAUL E
;    TITLE OF INVENTION:  GENETIC SEQUENCES AND PROTEINS RELATED
;    TITLE OF INVENTION:  TO ALZHEIMER'S DISEASE AND USES THEREFOR.
;    NUMBER OF SEQUENCES:  41
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  LERNER, DAVID, LITTENBERG, KRUMHOLZ & MENTLIK
;      STREET:  600 SOUTH AVENUE WEST
;      CITY:  WESTFIELD
;      STATE:  NJ
;      COUNTRY:  USA
;      ZIP:  07090-1497
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  ASCII
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/888,077A
;      FILING DATE:  03-JUL-1997
;      CLASSIFICATION:  530
;    PRIOR APPLICATION DATA:
;      APPLICATION NUMBER:  US 08/592,541
;      FILING DATE:  26-JAN-1996
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  PALISI, THOMAS M
;      REGISTRATION NUMBER:  36,629
;      REFERENCE/DOCKET NUMBER:  SCHERING 3.0-017 CIP CIP CIP IV
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  (908) 654-5000
;      TELEFAX:  (908) 654-7866
;  INFORMATION FOR SEQ ID NO:  2:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  467 amino acids
;      TYPE:  amino acid
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  protein
US-08-888-077A-2

  Query Match             100.0%;  Score 2393;  DB 2;  Length 467;
  Best Local Similarity   100.0%;  Pred. No. 7.1e-235;
  Matches  467;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQGNSR 60
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Db          1 MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQGNSR 60

Qy         61 QVVEQDEEEDEELTLKYGAKHVIMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTE 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 QVVEQDEEEDEELTLKYGAKHVIMLFVPVTLCMVVVVATIKSVSFYTRKDGQLIYTPFTE 120

Qy        121 DTETVGQRALHSILNAAIMISVIVVMTILLVVLYKYRCYKVIHAWLIISSLLLLFFFSFI 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 DTETVGQRALHSILNAAIMISVIVVMTILLVVLYKYRCYKVIHAWLIISSLLLLFFFSFI 180

Qy        181 YLGEVFKTYNVAVDYITVALLIWNFGVVGMISIHWKGPLRLQQAYLIMISALMALVFIKY 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 YLGEVFKTYNVAVDYITVALLIWNFGVVGMISIHWKGPLRLQQAYLIMISALMALVFIKY 240

Qy        241 LPEWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAE 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 LPEWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAE 300

Qy        301 GDPEAQRRVSKNSKYNAESTERESQDTVAENDDGGFSEEWEAQRDSHLGPHRSTPESRAA 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 GDPEAQRRVSKNSKYNAESTERESQDTVAENDDGGFSEEWEAQRDSHLGPHRSTPESRAA 360

Qy        361 VQELSSSILAGEDPEERGVKLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGLCL 420
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Db        361 VQELSSSILAGEDPEERGVKLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGLCL 420

Qy        421 TLLLLAIFKKALPALPISITFGLVFYFATDYLVQPFMDQLAFHQFYI 467
              |||||||||||||||||||||||||||||||||||||||||||||||
Db        421 TLLLLAIFKKALPALPISITFGLVFYFATDYLVQPFMDQLAFHQFYI 467
```

Franscis et al. Develop. Cell. 2002. 3: 85-97 as in IDS) teach a method of identifying RNAi that inactivates aph-1, pen-2 or nicastrin with presenilin and reduces gamma-secretase activity cleavage of APP and Notch.

Li et al. (PNAS 2000. 97: 6138-6143, as in IDS) teach a method of screening for an agent that modulates gamma-secretase activity using APP and presenilin-1.

13. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with

the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 5:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan, can be reached at (571) 272-0841.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/CYW/
Chang-Yu Wang, Ph.D.
August 30, 2007

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud